Chapter 105

IgA Nephropathy and Related Diseases

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Chapter Outline

INTRODUCTION

Since its initial description by Berger and Hinglais in 1968 (Berger and Hinglais, 1968), IgA nephropathy (IgAN) has been recognized as the most common glomerulonephritis worldwide (D'Amico et al., 1987; Julian et al., 1988) and an important cause of end-stage kidney failure (D'Amico, 2004). The incidence of IgAN varies greatly between countries, ranging as high as 40% of native-kidney biopsies in Asia, compared with about 20% in Europe, 5–10% in North America, and less than 5% in central Africa. The frequency for African Americans is similar to that for Caucasians in certain regions of the United States (Wyatt et al., 1998). Some of this variability in incidence may be due to differences in enthusiasm to undertake the invasive diagnostic procedure of renal biopsy in patients with relatively mild urinary abnormalities, although differences in genetically determined influences on the pathogenesis of the disease are also important (Gharavi et al., 2011; Kiryluk et al., 2012). The clinical and pathologic features of IgAN have been described in several extensive reviews (Barratt and Feehally, 2005; D'Amico, 2000; Donadio and Grande, 2002; Mestecky et al., 2013; Novak et al., 2012; Wyatt and Julian, 2013).

Recent studies have confirmed an autoimmune nature of IgAN and have led to a postulated multi-hit mechanism of disease (Suzuki et al., 2011) in which galactose (Gal)-deficient IgA1 is produced at elevated levels and is recognized by unique circulating anti-glycan autoantibodies. This process results in formation of immune complexes that, due to their large size, impair the usual hepatic clearance of IgA1. These IgA1-containing complexes ultimately reach the glomerular circulation to deposit in the mesangium and induce renal injury. Defective mucosal immunity has been implicated in the pathogenesis of IgAN because IgA1 synthesized in the mucosa normally contains Gal-deficient *O*-glycans in its hinge region (Boyd et al., 2012; Smith et al., 2006b).

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DISEASE PRESENTATION

Clinical Features

IgAN typically initially manifests in adolescence and young adulthood, but the first clinical evidence of renal disease may be observed in children as young as 4 years of age and adults older than 60 years. Hematuria and proteinuria are generally present, but the magnitudes of expression range widely. Macroscopic hematuria is the most dramatic clinical feature and is often concurrent with an infection of the upper respiratory tract (especially pharyngitis or tonsillitis) or gastrointestinal tract. This presentation is common in children and adolescents but rare in patients older than 40 years. Some patients have repetitive episodes of macroscopic hematuria and microscopic hematuria usually persists between these episodes. A second presentation, most common in adults, is asymptomatic microscopic hematuria that is usually accompanied by proteinuria. Such patients are often discovered to have renal disease during an annual examination or urinalysis testing for insurance or employment purposes. A third presentation is chronic renal insufficiency, presumably due to progressive kidney injury attributable to previously undiscovered disease. Proteinuria in the absence of hematuria is rare in IgAN. Nephrotic-range proteinuria is uncommon but may be found in patients with very active acute disease or advanced disease with substantial glomerular scarring.

Predictions of a benign long-term outcome in the early literature (McCoy et al., 1974) have proven to be incorrect. Persistent renal injury progresses to the point of necessitating renal replacement therapy by dialysis or transplantation within 20 years after the diagnostic biopsy in 20–40% of patients (D'Amico, 2004). The risk of end-stage renal failure has been recently associated with high levels of circulating antibodies specific for Gal-deficient glycans on IgA1 (Berthoux et al., 2012). Hypertension and proteinuria are two well-established prognostic factors and their control clearly improves the long-term outcome. An adverse impact for proteinuria begins with excretion rates as low as 500 mg per day (Le et al., 2012; Radhakrishnan and Cattran, 2012). As many as 20–25% of patients with preserved renal function enter a prolonged clinical remission, with normal serum creatinine concentration and normal urinalysis; nonetheless, repeat biopsy generally shows persistent glomerular IgA (Hotta et al., 2002). Some patients exhibit an indolent asymptomatic course, manifested as persistent or intermittent microscopic hematuria and modest proteinuria.

The immunohistological features of IgAN have also been documented in a surprisingly high fraction of the apparently healthy population. A study of renal donors in Japan showed that 82 (16%) of 510 allografts biopsied at the time of implantation had mesangial IgA deposits, with 8 (1.6%) exhibiting all of the immunohistological and light microscopic features typical of IgAN (Suzuki et al., 2003).

Genetically regulated mechanisms clearly influence the development or expression of IgAN. About 5% of patients have a first- or second-degree relative with biopsy-proven IgAN or clinical features of renal disease consistent with IgAN (Beerman et al., 2007). An elevated serum level of Gal-deficient IgA1 is a heritable trait (Gharavi et al., 2008) but is not sufficient to induce clinical IgAN. About 40–50% of first-degree relatives of patients with IgAN have an elevated level (Gharavi et al., 2008) without any urinary abnormality during prolonged observation. Genome-wide association studies have shown several loci that associate with IgAN, including (1) three loci in the major histocompatibility complex at chromosome 6p21 (Feehally et al., 2010; Gharavi et al., 2011); (2) a locus at chromosome 1q32 in the complement factor H gene cluster (Gharavi et al., 2011); (3) a locus at chromosome 22q12 (Gharavi et al., 2011) that encodes oncostatin M and leukemia inhibitory factor that are implicated in mucosal immunity and inflammation; (4) a locus at chromosome 17p23 in the segment that encodes a proliferation-inducing ligand (Yu et al., 2011); and (5) a locus at chromosome 8p23 in the defensin gene cluster (Yu et al., 2011). The specific associations differ between patients of different ethnicities but suggest that innate as well as adaptive immunity play significant roles in the pathogenesis of IgAN (Kiryluk et al., 2013; Mestecky et al., 2013).

Henoch-Schoenlein purpura with nephritis (HSPN) may represent the most overt manifestations of the autoimmune process that leads to IgAN. The renal immunopathological findings are the same as those of IgAN. The diagnosis of HSPN is frequently established clinically by the presence of a nephritic urinary sediment in a patient with the typical purpura. A skin biopsy shows a leukocytoclastic vasculitis with IgA in the walls of dermal capillaries (Davin, 2011; Davin et al., 2001; Davin and Weening, 2001). Identical histology has been shown for biopsies of clinically normal skin of some patients with IgAN (Waldherr et al., 1983). HSPN patients have a systemic IgA-induced vasculitis that frequently affects the gut, in addition to the kidneys. Multiplex families with siblings with IgAN and HSPN have been well described (Meadow and Scott, 1985), raising the possibility that the two diseases are separate manifestations arising from a shared mechanism of disease.

Pathologic Features

The diagnosis of IgAN is based on examination of renal cortical tissue using immunohistochemical techniques. IgA is the dominant or co-dominant immunoglobulin and is found primarily in the mesangium, even in glomeruli with normal appearance. The IgA is exclusively of the IgA1 subclass (Conley et al., 1980; Russell et al., 1986); IgA2 is not a factor in the genesis of IgAN. Complement component C3 is generally present in the same distribution

as IgA and is commonly accompanied by IgG, IgM, or both, although not with more intense immunofluorescence than that for IgA (Jennette, 1988). IgA is the sole immunoglobulin for as many as 60% of patients in some centers (Haas, 2007). Confocal microscopy has shown that when the immune deposits have an outer coat of C3 rather than IgA, the biopsy exhibits more severe glomerular damage (Muda et al., 1995). Components of the alternative pathway of complement activation are frequently detected, including properdin, and complement factors B and H. These findings, coupled with the presence of the C5b-9 complex, are consistent with an important role for complement activation in the process of renal injury of IgAN (Miyamoto et al., 1988). For other patients, activation of complement may be through the lectin pathway (Endo et al., 1998). On the other hand, components of the classical pathway are found only rarely; if C1q or C4 is present in a significant quantity, the possibility of lupus nephritis should be considered.

The light microscopic features of IgAN may vary greatly between patients with similar clinical manifestations and even within the biopsy specimen for an individual patient (Jennette, 1988). The histological hallmark of IgAN is focal (involving only some glomeruli) segmental (affecting only a portion of a given glomerulus) expansion of the mesangial area due to proliferation of resident mesangial cells and increased amounts of extracellular matrix. In patients with mild clinical disease, many of the glomeruli appear to be normal. However, in patients with more severe clinical disease, the mesangial proliferative activity produces a double-contouring or "tram-tracking" effect, usually leading to narrowing of the capillary lumen in the glomerular tuft. In patients with clinically active disease, manifested as significant microscopic, or even macroscopic, hematuria, there is often diffuse (involving all glomeruli) disease that may include necrosis of the glomerular tuft with an exudate of fibrin and infiltration of neutrophils. These features may be accompanied by a crescent in the Bowman space. The latter features are commonly accompanied by acute renal insufficiency. In patients with longstanding disease, some glomeruli exhibit areas of segmental tuft collapse and sclerosis that may arise by several mechanisms, including primary damage to podocytes, postinflammatory scarring, and compensatory hemodynamic changes. In progressive disease, this ongoing renal damage frequently culminates in glomerular obsolescence. As is the case for many other forms of glomerulonephritis, the tubular portion of the nephron and the surrounding interstitial area are frequently damaged by progressive IgAN. Based on a review of kidney biopsy specimens from patients with estimated glomerular filtration rate at least 30 mL/min per 1.73 m^2 and proteinuria greater than 0.5 g/day, an international panel of nephropathologists and nephrologists developed the Oxford classification of IgAN. Four light microscopic features showed independent value for predicting long-term outcome, even after accounting for clinical indicators assessed at the time of the biopsy (Cattran et al., 2009). Thus, in addition to establishing the diagnosis, a renal biopsy can provide useful prognostic information.

Ultrastructural examination of the glomeruli by electron microscopy shows varying degrees of proliferation of mesangial cells and expansion of the extracellular matrix with electron-dense deposits of differing size and amount. These deposits correspond to the immune proteins detected by immunohistochemical techniques. The electron-dense deposits are most commonly found in the paramesangial regions but are occasionally detected in the subendothelial and subepithelial areas of the glomerular basement membranes. The distribution and number of the deposits may be irregular, consistent with an episodic process for the deposition of immune complexes.

Secondary IgAN, a mesangial proliferative glomerulonephritis with IgA-dominant immunofluorescence in the setting of a nonrenal disease, has been described in patients with a wide variety of disorders. While some instances may reflect simply a chance overlap of IgAN with a physiologically unrelated process, other associations are likely due to a shared pathophysiological mechanism (Pouria and Barratt, 2008). The most commonly associated conditions include liver disease (alcoholic or virus-induced cirrhosis), inflammatory enteric diseases (ulcerative colitis, Crohn disease, and celiac disease), chronic infection (mucosal sites and skin), neoplasms, and connective tissue disorders. The postulated physiological mechanisms include failure of antigen exclusion or a dysregulated IgA immune response to antigen that prompts increased production of Gal-deficient IgA1, repetitive exposure to microbial cell-surface *N*-acetylgalactosamine (GalNAc) epitopes that elicits synthesis of antibody that cross-reacts with Gal-deficient *O*-glycans of the IgA1 hinge region, and failure to clear circulating nephritogenic IgA1 or IgA1-containing immune complexes (Pouria and Barratt, 2008; Tissandie et al., 2011). The pathologic features of secondary IgAN may differ from those of primary IgAN. In secondary IgAN, IgA1 is more likely to be the sole immunoglobulin in the mesangial immune deposits, C3 is less frequently present, and duplication of the glomerular basement membranes with mesangial interposition is more common (McGuire et al., 2006; Pouria and Barratt, 2008). It has not been clearly shown whether the mesangial IgA1 in secondary IgAN is Gal-deficient as is the IgA1 in primary IgAN (Pouria and Barratt, 2008), although as of this writing some recent findings suggest abnormalities in *O*-glycans as well as *N*-glycans in at least some patients with secondary IgAN (Tissandie et al., 2011). The clinical expression of secondary IgAN, as manifested by proteinuria and microscopic hematuria, frequently parallels the activity of the inciting nonrenal disease.

STRUCTURE AND SUBCLASSES OF HUMAN IgA

Serum IgA in humans consists of IgA1 (~85% of total IgA) and IgA2 (~15% of total IgA), and both subclasses are predominantly monomers (see Chapter 17). IgA1 dominance in serum mirrors the proportion of IgA1-producing cells in the bone marrow, whereas in external secretions, the proportion of IgA1 to IgA2 reflects the distribution of IgA1- and IgA2-secreting cells in corresponding mucosal tissues (Pakkanen et al., 2010). For example, the respiratory and upper intestinal tracts contain more IgA1- than IgA2-producing cells, whereas the large intestine exhibits a slight dominance of IgA2-producing cells (see Chapter 17).

IgA can form polymers due to the *C*-terminal 18 amino acid sequence with cysteine that binds joining (J) chain. Polymeric (i.e., J-chain-containing) IgA binds to the epithelial polymeric immunoglobulin receptor (pIgR) that mediates the transepithelial transport of locally produced IgA into external secretions (see Chapter 20). In sera of healthy individuals, a small proportion (~1–2%) of IgA is present in a polymeric form with J chain.

The heavy chains of IgA1 and IgA2 are quite similar in the primary structures, except for the hinge-region segment between constant-region domains 1 and 2 of the heavy chains (CH1 and CH2). The hinge region of human IgA2 consists of 13 amino acid residues, whereas in IgA1 it has 26 amino acid residues (Frangione and Wolfenstein-Todel, 1972; Putnam, 1989; see Chapter 17). The hinge region of IgA1 resembles mucins with its high content of serine and threonine residues. As in mucins, the IgA1 hinge region has clustered *O*-glycans (Figure 1).

Notably, IgA1 is susceptible to proteolytic cleavage by unique IgA1-specific proteases produced by several pathogenic bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, and others (Kilian et al., 1996; see Chapter 23). IgA1-specific proteases are serine proteases, metalloproteases, or cysteine proteases (Kilian et al., 1980; see Chapter 23) that cleave a peptide bond between a specific proline and serine/threonine, resulting in the production of Fc and Fab fragments. IgA1-specific proteases are thus considered virulence factors (see Chapter 23).

The extended hinge region of IgA1 confers added segmental flexibility and, therefore, increases the antigen-binding capacity (Jarvis and Griffiss, 1991). Relevant functional and structural differences between human IgA1 and IgA2 are reflected by their different specificities (Bonner et al., 2009). In general, IgA antibodies specific for proteins and glycoproteins of microbial origin are present dominantly in the IgA1 subclass whereas IgA antibodies directed against polysaccharides, lipopolysaccharides, and lipoteichoic acid are in the IgA2 subclass (Bonner et al., 2009; see Chapter 17). Thus, it appears that the character of an antigen influences the immune response with respect to the IgA subclass.

SYNTHESIS AND CATABOLISM OF IgA

In healthy adults, the daily production of IgA (approximately 70 mg/kg/day) exceeds that of all other immunoglobulins combined (Conley and Delacroix, 1987; see Chapter 17).

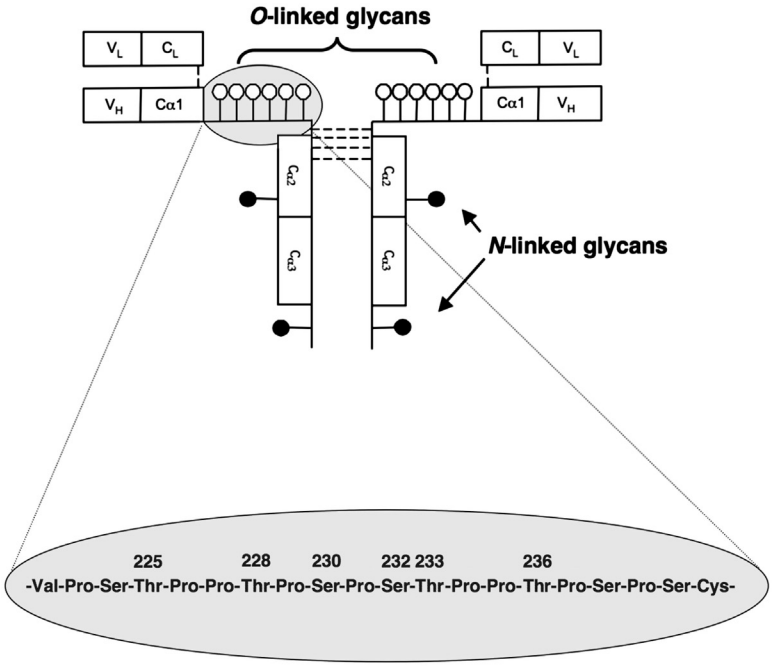

FIGURE 1 Structure of human IgA1. Monomeric form of IgA1: each heavy chain has two *N*-glycans and three to six *O*-glycans. A variant with six *O*-glycans per hinge region is shown. Hinge-region segment, the site of *O*-glycan attachment, is marked by a gray oval for one heavy chain. Amino acid sequence of the hinge region of human IgA1 is shown in gray oval. Amino acid residues are numbered to mark the six common sites of *O*-glycan attachment. *Takahashi et al., 2012, 2010.*

Most IgA is produced in mucosal tissues, where a pIgR-mediated pathway selectively transports it into the secretions and only trace amounts enter the circulation (Mestecky et al., 1989, 1986; see Chapter 17). Circulatory IgA originates mainly from the bone marrow and, to a lesser extent, from the spleen and lymph nodes. The elevated levels of IgA in sera of IgAN patients may be due to an imbalance between increased production on one hand and altered clearance and catabolism on the other. The increased levels of total serum IgA appear to be due to the elevation of IgA1 in its polymeric, J chain-associated form (Harper et al., 1995; Jones et al., 1990; Layward et al., 1992; Leung et al., 2002a; Tomana et al., 1999). However, the tissue origin of this IgA remains unclear. Based on the well-established sites of the production of various molecular forms of IgA, including the proportions of monomeric versus polymeric IgA and IgA subclasses in different human tissues (see Chapter 17), it is probable that IgA1-producing cells in the mucosal tissues, especially in the respiratory and upper digestive tracts, are the main source. Normal human serum contains only small amounts of pIgA. In IgAN patients, the increase in circulatory pIgA may be due to higher production or the presence of circulating immune complexes (Layward et al., 1992; Leung et al., 2002a; Tomana et al., 1999). Molecular studies of the properties and composition of circulating immune complexes indicated a heterogeneity with respect to the molecular mass (Novak et al., 2005). IgA in circulating immune complexes was exclusively of the IgA1 subclass and dominantly of the polymeric form. Other components detected in circulating immune complexes were C3 complement component and IgG; IgM was found only rarely (Czerkinsky et al., 1986). Importantly, the composition of circulating immune complexes parallels that of the mesangial deposits, including the presence of Gal-deficient pIgA1, C3, and frequently IgG. Circulating immune complexes and mesangial deposits may share common but not disease-specific idiotypic determinants (van den Wall Bake et al., 1993). These results, as well as the demonstrated nephritogenic activity of immune complexes generated in vitro, indicate that immune complexes in the mesangium are likely deposited from the circulation (Suzuki et al., 2011).

The lower serum levels of IgA than IgG are due to the significantly shorter circulatory half-life (4–5 days for IgA vs 21 days for IgG) and the distribution of IgA in various body fluids; about two thirds of IgA is transported by a receptor-mediated mechanism into external secretions (see Chapter 20). Circulatory IgA is catabolized predominantly in the liver by hepatocytes (Baenziger and Fiete, 1980, 1982; Baenziger and Maynard, 1980; Moldoveanu et al., 1988, 1990; Phillips et al., 1988, 1984; Stockert, 1995; Stockert et al., 1982; Tomana et al., 1988, 1985). Interactions of IgA1 as well as IgA2 with hepatocytes is mediated by the asialoglycoprotein receptor (ASGP-R), which recognizes terminal Gal of *N*-glycans of IgA1 and IgA2 and terminal Gal as well as terminal GalNAc on *O*-glycans of IgA1 (Ashwell and Harford, 1982; Baenziger and Fiete, 1980; Baenziger and Maynard, 1980; Stockert, 1995; Stockert et al., 1982; Tomana et al., 1988, 1985). A smaller percentage of circulatory IgA is catabolized by hepatic nonparenchymal cells and by muscles, skin, spleen, and kidneys.

ASGP-R is a recyclable receptor. In the presence of bivalent cations it recognizes glycoproteins with terminal Gal or GalNAc residues, including IgA (Baenziger and Fiete, 1980). Therefore, the Gal deficiency on IgA1 should not substantially impair the IgA1 catabolism because GalNAc is exposed. This conclusion would be valid for free monomeric IgA1 and polymeric IgA1 molecules. However, this mechanism of clearance is altered for circulating immune complexes due to their physicochemical properties. To interact with the ASGP-R on hepatocytes, glycoproteins exit the circulation through the porous endothelial barrier into the space of Disse. Importantly, the fenestrae in the endothelial cells permit the exit of molecules with a molecular mass of less than 1000 kDa (Socken et al., 1981) and appropriate molecular dimensions. Molecules with a larger molecular mass, including circulating immune complexes, do not have access to ASGP-R and remain in the circulation. They may deposit in other tissues, including the kidney, where the larger endothelial fenestrae in the glomerular capillaries permit penetration of high-molecular-mass circulating immune complexes.

The molecular mass of Gal-deficient pIgA1 (~340 kDa) is significantly increased in circulating immune complexes due to the IgG (or IgA1) antibodies specific for the altered hinge-region glycans. Consequently, the antibody limits interaction of the terminal GalNAc residues with the ASGP-R on hepatocytes and reduces the clearance of the Gal-deficient IgA1 from the circulation.

GLYCOSYLATION OF CIRCULATORY IgA1

Each heavy (H) chain of human IgA1 contains two *N*-glycans in the Fc portion, one at Asn263 and the second at Asn459 in the tailpiece portion (Figure 1). The Asn263 site contains a biantennary glycan with or without a bisecting *N*-acetylglucosamine (GlcNAc) that is usually not fucosylated. In contrast, the tailpiece Asn459 site contains a fucosylated glycan (Gomes et al., 2008; Tanaka et al., 1998).

IgA1 H chains also contain a hinge-region segment with three to six *O*-glycans (Figure 1). Hinge-region glycoforms with four and five glycans are the most common (Iwase et al., 1998; Mattu et al., 1998; Renfrow et al., 2005, 2007; Takahashi et al., 2010; Tarelli et al., 2004; Wada et al., 2010). Normal human IgA1 in the circulation has core 1 *O*-glycans consisting of GalNAc with β1,3-linked Gal. Each saccharide can be sialylated, GalNAc with an α2,6 linkage and Gal with an α2,3 linkage. The carbohydrate composition of the *O*-linked glycans is variable and the prevailing forms include the GalNAc-Gal disaccharide and its mono- and disialylated forms (Figure 2) (Baenziger and Kornfeld, 1974;

Field et al., 1989; Mattu et al., 1998; Tomana et al., 1972, 1976, 1978).

O-GLYCOSYLATION OF IgA1 IN IgAN

It has been known for some time that IgA1 *O*-glycans in patients with IgAN are altered (Allen et al., 1995; Andre et al., 1990; Mestecky et al., 1993; Moldoveanu et al., 2007; Tomana et al., 1997). Specifically, some circulatory IgA1 molecules have some *O*-glycans without Gal, i.e., consisting of terminal GalNAc or sialylated GalNAc (Figure 2, first two structures). This galactosylation defect is specific for IgA1, as other *O*-glycosylated glycoproteins in sera of patients with IgAN do not exhibit this abnormality (Allen et al., 1995; Smith et al., 2006a). Normal serum IgA1 had been thought to contain few or no Gal-deficient *O*-glycans (Mattu et al., 1998), but later studies showed that Gal-deficient *O*-glycans may be present at Ser230, Thr 233, and/or Thr 236 (Figure 1) (Takahashi et al., 2012). These data fit well with the earlier observations that GalNAc-specific lectins, such as agglutinin from *Helix aspersa*, bind small amounts of IgA1 from healthy controls (Allen et al., 1995; Moldoveanu et al., 2007; Tomana et al., 1997, 1999). A quantitative lectin ELISA confirmed that patients with IgAN have elevated serum levels of Gal-deficient IgA1 compared to healthy controls (Lau et al., 2007; Moldoveanu et al., 2007; Shimozato et al., 2008; Zhao et al., 2012). Most Gal-deficient IgA1 is in circulating immune complexes bound by anti-glycan IgG or IgA1 antibodies (Tomana et al., 1999).

Analytical approaches for studies of IgA1 *O*-glycosylation used lectins (glycan-specific proteins), Edman sequencing, monosaccharide compositional analysis by gas–liquid chromatography, and various types of mass-spectrometric analyses. Direct localization of sites of *O*-glycan attachment on IgA1 can be accomplished with electron capture dissociation (ECD) or electron transfer dissociation (ETD) tandem mass spectrometry using hinge-region glycopeptides generated by proteolytic cleavage (Renfrow et al., 2005, 2007; Takahashi et al., 2012, 2010; Wada et al., 2010). Individual hinge-region glycoforms are identified by their molecular mass and the sites of *O*-glycan attachment are determined by ECD or ETD dissociation, a process that fragments glycopeptides while leaving glycans attached to the amino acid backbone. These analytical approaches also identified *O*-glycoform isomers, i.e., IgA1 isoforms with same number of glycans but different sites of attachment for some of them. Moreover, Gal-deficient glycans were found most commonly at Ser230, Thr233, and/or Thr236 in different combinations in normal serum IgA1 and in IgA1 myeloma proteins. Future studies will need to define IgA1 *O*-glycosylation in the context of adjacent sites as well as the heterogeneity at each individual site and assess differences in *O*-glycans on IgA1 from IgAN patients as compared to that from controls. Such studies should also determine whether any specific glycoforms(s) is associated with disease severity and/or progression.

BIOSYNTHESIS OF IgA1 *O*-GLYCANS

Much of the information about *O*-glycosylation pathways came from studies of mucins in secretions, cell membrane-associated mucins (such as MUC1) in normal cells and in cancer, and examination of *O*-glycan synthesis on blood cell glycoproteins in patients with a rare disease called Tn syndrome (for reviews, see Berger (1999), Gerken et al. (2011), Ju and Cummings (2005), Ju et al. (2011), Tarp et al. (2007), Thurnher et al. (1993), and Vainchenker et al. (1985)). However, information relevant to *O*-glycosylation pathways of IgA1 in IgAN was generated based on studies of cells secreting IgA1 (Buck et al., 2008; Itoh et al., 2003; Ju et al., 2002; Lin et al., 2009; Qin et al., 2005; Raska et al., 2007; Suzuki et al., 2008a; Tokuda et al., 1996; Yamada et al., 2010).

Initiation of *O*-glycosylation of IgA1 is thought to be mediated primarily by GalNAc-transferase 2 (GalNAc-T2) (Iwasaki et al., 2003) but other GalNAc-Ts may contribute to the process (Wandall et al., 2007) (Figure 3). In fact, not only GalNAc-T2 (Suzuki et al., 2011, 2008a) but other GalNAc-Ts are abundantly expressed in IgA1-producing cells derived from the circulation of IgAN patients and healthy controls (Stuchlova Horynova et al., 2013). Specifically, GalNAc-T14, the closest structural relative of GalNAc-T2,

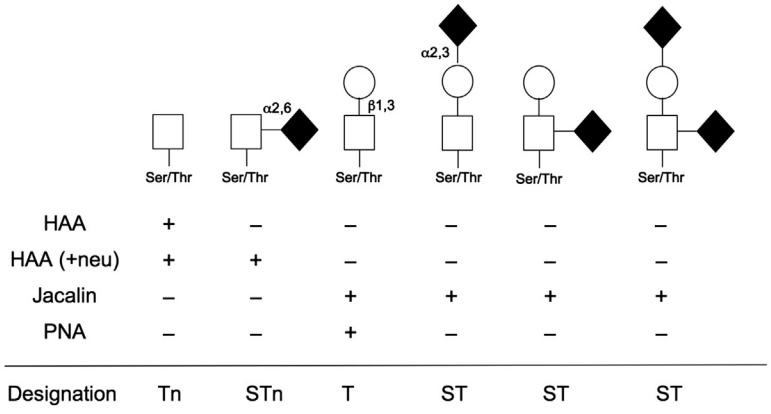

FIGURE 2 ***O*-glycans of circulatory IgA1.** The first two structures on the left are Gal-deficient *O*-glycans, whereas other structures represent galactosylated variants with or without sialic acid. GalNAc-specific and GalNAc-Gal-specific lectins and their reactivities with IgA1 *O*-glycan variants are shown (Allen, 1999; Allen et al., 1995; Field et al., 1989; Gomes et al., 2010; Moore et al., 2007; Suzuki et al., 2008a; Tomana et al., 1997). Designation of the glycan structures is shown: Tn, Tn antigen; STn, sialyl Tn antigen; T, T antigen; ST, sialyl T antigen. Symbols: square, GalNAc; circle, Gal; diamond, sialic acid. Neu, neuraminidase; HAA, *Helix aspersa* agglutinin; PNA, peanut agglutinin; jacalin, lectin from jackfruit.

was among the major GalNAc-Ts transcribed in IgA1-producing cells and its expression was severalfold greater in the cells from IgAN patients compared to the expression in the cells from healthy controls. Conversely, the expression of GalNAc-T2 and other GalNAc-Ts did not differ between patients and healthy controls.

After GalNAc is attached, Gal may be added to produce the core 1 *O*-glycan GalNAc-Gal. This reaction is catalyzed by a unique β1,3-galactosyltransferase (C1GalT1) (Figure 3) (Ju et al., 2002, 2011) and the lack of C1GalT1 results in truncated *O*-glycans (Wang et al., 2010). In patients with IgAN, several groups have found downregulated expression of C1GalT1 (Allen et al., 1997; Novak et al., 2012; Serino et al., 2012; Stuchlova Horynova et al., 2013; Suzuki et al., 2008a).

Expression of C1GalT1 protein depends on a specific chaperone (Cosmc) (Figure 3) (Ju and Cummings, 2002, 2005; Ju et al., 2011). Cosmc is mutated in several cell lines (e.g., T cell line Jurkat) and in some types of cancer (for review, see Ju et al. (2011)). Cosmc mutation is one of the mechanisms that lead to expression of terminal GalNAc (also called Tn antigen) and sialylated GalNAc (also called STn antigen) in cancer. Cosmc may be also downregulated by epigenetic mechanisms (Mi et al., 2013). Notably, the Jurkat cell line with Cosmc mutation reverted to core 1 synthesis when SHIP-1 (Src homology 2-containing inositol 5′-phosphatase-1) was expressed, suggesting that the requirement of Cosmc for the production of active C1GalT1 can be bypassed by another mechanism (Charlier et al., 2010). The level of Cosmc expression in IgA1-producing cells from IgAN patients and the role of Cosmc in production of Gal-deficient IgA1 are still to be precisely determined (Malycha et al., 2009; Qin et al., 2008; Suzuki et al., 2011, 2008a; Yamada et al., 2010).

In normal IgA1, some core 1 structures are modified by attachment of sialic acid to Gal in a reaction catalyzed by a Galβ1,3GalNAc α2,3-sialyltransferase (ST3Gal) and/or by attachment of sialic acid to the GalNAc residues catalyzed by α2,6-sialyltransferase (Figure 3) (ST6GalNAc-II) (for review, see Stuchlova Horynova et al. (2013)).

The biosynthetic basis for aberrant IgA1 *O*-glycosylation (i.e., synthesis of Tn antigen) in IgAN has been extensively studied and, although progress has been made, there are still many open questions (Mestecky et al., 2013; Novak et al., 2012; Stuchlova Horynova et al., 2013). Studies with IgA1-producing cells from patients with IgAN showed that they secreted polymeric IgA1 with exposed terminal GalNAc, i.e., Tn antigen (Raska et al., 2007; Suzuki et al., 2009). Neuraminidase treatment of the secreted IgA1 markedly enhanced reactivity with a GalNAc-specific lectin, suggesting that some Tn *O*-glycans are capped with sialic acid, i.e., sialyl-Tn antigen. These glycosylation aberrancies were associated with altered expression of specific genes elevated expression of *ST6GALNAC2* and decreased expression of *C1GALT1* and *Cosmc* (Suzuki et al., 2008a). These results were consistent with the measured enzyme activities in cell extracts. The observed decrease in expression of *Cosmc* would potentially further reduce the amount of intact C1GalT1 enzyme due to degradation of C1GalT1 in the absence of its protein chaperone.

Another factor that may affect *O*-glycosylation of IgA1 is the relative localization of the specific glycosyltransferases within the Golgi apparatus and/or the turnover of some glycosyltransferases (Stuchlova Horynova et al., 2013). Moreover, premature sialylation of GalNAc would block, or at least significantly hinder, further modifications. The observation that IgA1 with sialylated GalNAc is present throughout the Golgi (Suzuki et al., 2008a) lends support to the notion of an abnormal localization of the ST6GalNAc-II sialyltransferase. Future studies are needed to characterize subcellular localization of individual enzymes as well as to characterize the ST6GalNAc-II and C1GalT1 enzymes for their substrate specificities and kinetics by using various IgA1 hinge-region glycoforms as acceptors.

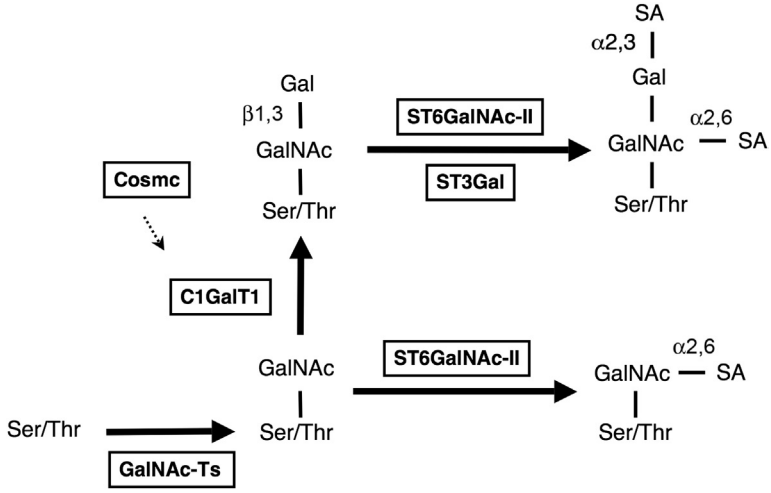

FIGURE 3 Biosynthesis of *O*-glycans of circulatory IgA1. *O*-glycan synthesis of circulatory IgA1 begins with addition of GalNAc to hinge-region Ser/Thr residues by GalNAc-transferases. Three to six GalNAc residues are attached per hinge region (Takahashi et al., 2012, 2010). Gal and/or sialic acid residues can be then added. The addition of Gal is catalyzed by core 1 β1,3-galactosyltransferase (C1GalT1). Production of active C1GalT1 protein depends on interaction with its chaperone (Cosmc). Without Cosmc, the C1GalT1 protein is rapidly degraded. The glycan structure is completed by sialyltransferases that attach sialic acid to the Gal (ST3Gal) and/or GalNAc (ST6GalNAc-II) residues. If sialic acid is attached to GalNAc before galactosylation, Gal cannot be added.

PATHOGENIC PATHWAYS IN IgAN

Studies since the late 1990s defined IgAN as an autoimmune disease, in which Gal-deficient IgA1 is an autoantigen (Suzuki et al., 2008a; Tomana et al., 1997, 1999) that is recognized by IgG and IgA1 autoantibodies specific for GalNAc-containing epitopes on Gal-deficient IgA1 (Suzuki et al., 2009; Tomana et al., 1999). We have formulated a multi-hit theory for pathogenetic pathways of IgA1 (Figure 4). IgA1 molecules that have some Gal-deficient *O*-glycans (hit 1) are recognized by anti-glycan antibodies with unique antigen-binding sites (hit 2) (Suzuki et al., 2009, 2011). These two hits are likely related to abnormal mucosal immune system in patients with IgAN that may promote production of Gal-deficient IgA1 and/or anti-glycan antibodies (Kiryluk et al., 2013; Mestecky et al., 2013; Novak et al., 2012, 2011a). Such processes result in formation of nephritogenic immune complexes (hit 3) (Novak and Mestecky, 2009; Novak et al., 2011a,b; Suzuki et al., 2009; Tomana et al., 1999). These complexes are relatively large (Novak et al., 2005, 2002; Tomana et al., 1997, 1999), are not efficiently cleared from the circulation, tend to deposit in the renal mesangium, and bind to mesangial cells and activate them, leading to renal injury (hit 4) (Mestecky et al., 2013; Novak et al., 2012; Suzuki et al., 2011). Activated mesangial cells proliferate and overproduce components of extracellular matrix and multiple cytokines (Gomez-Guerrero et al., 1995; Novak and Mestecky, 2009; Novak et al., 2011b, 2005; Tamouza et al., 2012). Subsequently, some cytokines (e.g., TNF-α, TGF-β) may alter podocyte gene expression and thus glomerular permeability (Lai et al., 2008, 2009), leading to proteinuria and tubulointerstitial injury. Complement activation by IgA–IgG complexes is likely an important feature in the pathogenetic pathways (Waldo and Cochran, 1989).

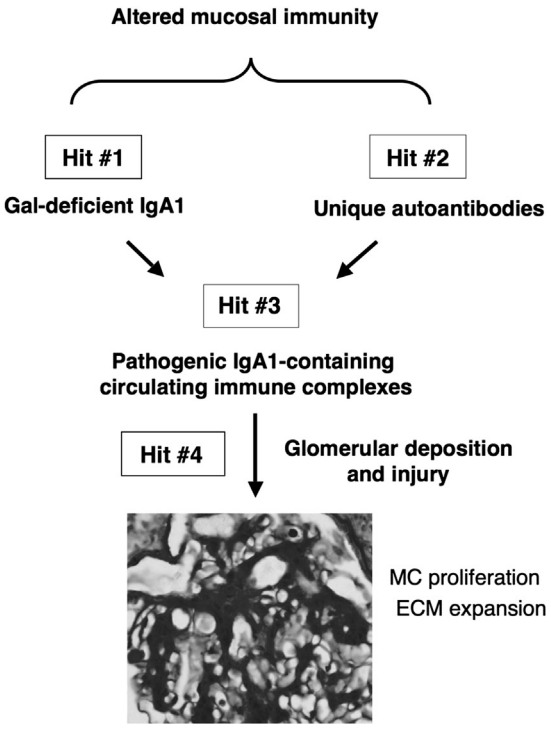

FIGURE 4 Pathogenesis model for IgAN. This model assumes formation of IgA1-containing immune complexes in the circulation and their subsequent mesangial deposition. Hit 1: Increased production of Gal-deficient IgA1 by a subpopulation of IgA1-secreting cells (Suzuki et al., 2008a). Hit 2: Formation of autoantibodies with specific characteristics of the variable region of the heavy chain that recognize Gal-deficient IgA1 (Suzuki et al., 2009). Hit 3: Formation of nephritogenic immune complexes from autoantigen (Gal-deficient IgA1) and autoantibody (Novak et al., 2011b, 2005). Hit 4: Deposition of nephritogenic immune complexes in the mesangium activates mesangial cells and induces glomerular injury (Lai et al., 2008, 2009; Leung et al., 2008, 2002b; Moura et al., 2004; Novak et al., 2011b, 2005). In addition, there are upstream factors associated with abnormal mucosal immune responses characteristic for IgAN patients (Bene et al., 1991; Smith et al., 2006b; Suzuki et al., 2008b) and these factors, as well as hits 1–4, are influenced by multiple genetic loci (Beerman et al., 2007; Feehally et al., 2010; Gharavi et al., 2011, 2008; Izzi et al., 2006; Kiryluk et al., 2010, 2012, 2011, 2013; Lavigne et al., 2010; Mestecky et al., 2013; Suzuki et al., 2011; Yu et al., 2011). MC, mesangial cells; ECM, extracellular matrix.

The key role of IgA1-containing immune complexes in the pathogenesis of IgAN has been supported by multiple lines of evidence. Indication that the primary cause of IgAN is extrarenal includes the recurrence of the disease in approximately 50–60% of patients who receive a new kidney (Berger, 1988; Coppo et al., 1995a,b; Odum et al., 1994). Moreover, in the few cases in which a kidney was transplanted from a donor with subclinical IgAN into a patient with non-IgAN renal disease, clearance of the immune deposits from the affected kidney was observed within several weeks (Silva et al., 1982).

It is well established that patients with IgAN have elevated levels of IgA and IgA1-containing immune complexes in the circulation (Coppo et al., 1984; Czerkinsky et al., 1986; Schena et al., 1989; Tomana et al., 1997). Idiotypic determinants are shared between the circulating complexes and the mesangial deposits (Gonzales-Cabrero et al., 1989), although a disease-specific idiotype has not been identified (van den Wall Bake et al., 1993). Early studies clearly demonstrated that the circulating immune complexes in patients with IgAN contain IgA1 (Coppo et al., 1982; Czerkinsky et al., 1986; Tomana et al., 1999). More recently, it was found that Gal-deficient IgA1 is the predominant glycosylation variant of IgA1 in the mesangium (Allen et al., 2001; Hiki et al., 2001) and that circulating immune complexes in patients with IgAN contain Gal-deficient IgA1 (Novak et al., 2005, 2002; Tomana et al., 1997, 1999).

A relationship between a Gal deficiency and nephritis also has been observed in other diseases. Gal-deficient IgA1 (Greer et al., 1998) and IgA-IgG circulating complexes (Levinsky and Barratt, 1979) are found in sera of patients with Henoch-Schoenlein purpura who develop nephritis but not in sera of patients without urinary abnormalities. Also,

patients with IgA1 myeloma have high levels of circulating IgA1 but only those with aberrantly glycosylated IgA1 develop immune-complex glomerulonephritis (van der Helm-van Mil et al., 2003; Zickerman et al., 2000).

The hypothesis on the significance of IgA1-containing immune complexes in the pathogenesis of IgAN has also been supported experimentally, using cultured human mesangial cells as an experimental model. In this model, IgA1-containing immune complexes from sera of IgAN patients stimulated cellular proliferation. This conclusion was supported by control experiments in which IgA1-depleted fractions were devoid of such stimulatory complexes (Novak et al., 2007, 2011b, 2005). Conversely, when sera of IgAN patients were supplemented with Gal-deficient IgA1, additional stimulatory IgA1-containing immune complexes were formed (Novak and Mestecky, 2009; Novak et al., 2007, 2011b, 2005) but uncomplexed Gal-deficient IgA1 did not induce cellular proliferation (Novak and Mestecky, 2009; Novak et al., 2007, 2011b; 2005; Yanagihara et al., 2012).

Identification of cellular receptors and downstream pathways involved in the binding of IgA1 and IgA1-containing complexes and activation of mesangial cells has been the subject of multiple studies. Several studies found that a specific IgA receptor(s) expressed by mesangial cells binds and contributes, at least partially, to internalization of IgA1 (Moura et al., 2004, 2001; Novak et al., 2002; Tamouza et al., 2012, 2007). It has been shown that transferrin receptor (CD71) binds polymeric IgA1 and IgA1-containing immune complexes and is involved in activation of human mesangial cells (Kanamaru et al., 2007; Matysiak-Budnik et al., 2008; Moura et al., 2005, 2004, 2001; Tamouza et al., 2012). Another IgA1-binding receptor(s) was recently described as integrins α1/β1 and α2/β1 (Kaneko et al., 2012). Several studies have shown that IgA1 and IgA1-containing immune complexes induce protein tyrosine kinase-mediated signaling in human mesangial cells (Huang et al., 2012; Kaneko et al., 2012; Novak et al., 2011b; Tamouza et al., 2012). It is hoped that mapping the pathways may provide targets for a disease-specific therapy of IgAN.

GLYCAN DEFICIENCIES IN OTHER DISEASES

A growing body of evidence indicates that glycans on free or cell-bound glycoproteins participate in many biological functions and that several human diseases of autoimmune character are associated with alterations of glycan moieties. Current studies of glycan deficiency in IgAN were in part inspired by detailed molecular, cellular, and genetic studies of a rare human disease—Tn syndrome, also called mixed field polyagglutinability—in which surface glycoprotein on platelets, erythrocytes, and myeloid and/or lymphoid cells display deficiency of Gal in *O*-linked glycans (Berger, 1999). These glycoproteins are recognized by naturally occurring anti-GalNAc antibodies mostly of the IgM isotype, as manifested in vitro by agglutination of blood elements or in vivo by damage to any types of cells deficient in Gal. However, this disease displays clinical manifestations only when 10% or more of blood elements exhibit Gal deficiency. In this respect, Tn syndrome is analogous to IgAN because circulating immune complexes may also be detected in the circulation of individuals without any clinically apparent manifestation. Gal deficiency can also occur in *N*-linked glycans of IgG isolated from sera of patients with chronic inflammatory diseases such as rheumatoid arthritis, Sjögren syndrome, inflammatory bowel diseases, and periodontal disease, and is exhibited particularly strongly on IgG from sera of HIV-1-infected individuals (Mestecky et al., 2013; Moore et al., 2005). Gal deficiency on heavy chains of IgG molecules results in the exposure of terminal GlcNAc, which leads to an effective activation of the lectin pathway of the complement cascade with ensuing inflammation. Thus, it is apparent that glycan alterations are commonly found in human diseases of medical importance.

POSSIBLE APPROACHES FOR DEVELOPING DISEASE-SPECIFIC TREATMENT AND BIOMARKERS

Currently, there is no disease-specific treatment of IgAN and, thus, the primary emphasis is to ameliorate glomerular permeability and scarring by suppressing angiotensin II, with supporting therapy to control blood pressure (Floege and Eitner, 2011). It is hoped that elucidating the complete pathogenetic pathways of IgAN will provide suitable targets for developing disease-specific therapy as well as new markers with diagnostic and/or prognostic significance.

The multi-hit model (Figure 4) provides a framework for more precise considerations. Specifically, nephritogenic immune complexes that are composed of Gal-deficient IgA1 and anti-glycan autoantibodies insult the glomerular resident cells and initiate disease processes. Based on these assumptions, approaches that would reduce production of Gal-deficient IgA1 or anti-glycan antibodies or prevent formation of the large-molecular-mass Gal-deficient IgA1-containing immune complexes or reduce their nephritogenic activity can be considered (for details, see these reviews: Mestecky et al. (2013), Novak et al. (2012), Novak and Mestecky (2009), and Suzuki et al. (2011)).

Similar considerations are valid for developing genetic and biochemical markers of IgAN, including those for disease severity and prediction of disease progression. Examples of potential biochemical markers are elevated levels of Gal-deficient IgA1 or its specific glycoforms or elevated levels of glycan-specific IgG and IgA1 autoantibodies (Suzuki et al., 2011). A quantitative lectin ELISA (Gomes et al., 2010; Moldoveanu et al., 2007) showed that elevated levels of Gal-deficient IgA1 correlated with worse clinical

outcomes and poor prognosis (Zhao et al., 2012). In the future, high-resolution mass spectrometric approaches may provide information about specific glycoform(s) of Gal-deficient IgA1 that has pathogenic potential (Takahashi et al., 2012, 2010).

Measurements of IgG and IgA1 autoantibodies specific for Gal-deficient IgA1 also showed promise as potential biomarkers. Elevated serum levels of IgG autoantibody correlated with proteinuria in patients with IgAN (Suzuki et al., 2009). Moreover, serum levels of these IgG and IgA autoantibodies are associated with progression of IgAN (Berthoux et al., 2012). These conclusions are further supported by the association between presence and intensity of staining for IgG in renal biopsy specimens and serum levels of Gal-deficient IgA1 (Eison et al., 2012). An absence of IgG in the biopsy was weakly associated with normal serum levels of Gal-deficient IgA1 (Eison et al., 2012). Conversely, IgG deposition is recognized as a risk factor for persistent urinary abnormalities associated with the development of proliferative changes in IgAN (Bellur et al., 2011).

Another type of biomarkers is represented by urinary proteins and peptides (for review, see Fliser et al. (2007), Julian et al. (2009a), (2009b), and Mischak et al. (2009)). Towards this goal, a urinary peptidome, a set of human urinary peptides and small proteins, has been analyzed (Good et al., 2010). The urinary peptidome is represented by approximately 5010 unique peptides that can serve as a pool of potential markers for diagnosis and monitoring of various diseases, as demonstrated in several clinical studies (Haubitz et al., 2005; Julian et al., 2007; Mischak et al., 2010a, 2012, 2010b; Rossing et al., 2008). Such approaches may become routinely available in the future as part of clinical laboratory panels aiding in the assessment of disease activity and responses to treatment (Julian et al., 2009a; Mischak et al., 2010a, 2012).

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